Remarks

Claim Amendments

Claim 1 is amended to recite a composition "for selectively labeling a target cell." A corresponding amendment is made to claim 8. See page 5, lines 5-6 of the specification: "Selective localization and retention of radiolabel within a class of target cells is increased using such oligopeptides."

New claim 48 is supported by originally filed claim 8. Minor clarifying amendments have been made to dependent claims 5-8 and 10.

The amendments do not add new matter.

The Rejection of Claims 1-9, 11-21, and 44-47 Under 35 U.S.C. § 112, first paragraph

Claims 1-9, 11-21, and 44-47 stand rejected under 35 U.S.C. § 112, first paragraph, as insufficiently described in the specification. Applicant respectfully traverses the rejection.

Independent claim 1 and dependent claims 2-9, 11-21, and 44-47 each recite a ligand which specifically binds to a surface antigen of a cell and which is internalized by the cell. The ligand can be an antibody, a fragment of an antibody, or a synthetic polypeptide. The Office Action asserts that the specification does not provide sufficient support for the genus of antibody fragments or the genus of synthetic polypeptides.

The first paragraph of 35 U.S.C. § 112 requires that the specification provide a written description of the claimed invention:

> [t]he specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the

best mode contemplated by the inventor of carrying out his invention.

The purpose of the written description requirement is to ensure that the specification conveys to those skilled in the art that the applicants possessed the claimed subject matter as of the filing date sought. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2d (BNA) 1111, 1117 (Fed. Cir. 1991). The present specification meets this standard.

The specification adequately describes the recited genus of antibody fragments. The specification teaches that [i]f a fragment of an antibody is used, the fragment should be capable of binding to a cell surface antigen." Page 6, lines 12-14. The specification also teaches that the antibody fragment "can comprise, for example, at least a portion of an immunoglobulin light chain variable region and at least a portion of an immunoglobulin heavy chain variable region."

What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail to satisfy the written description requirement. M.P.E.P. 8th ed., § 2163(II)(A)(3)(a). The recited genus of antibody fragments were conventional and well known in the art when the present application was filed. At that time, well known antibody fragments included Fab fragments, Fab' fragments, and $F(ab')_2$ fragments. See Abbas, Cellular and Molecular Immunology, W. B. Saunders, Philadelphia, PA, 1997, page 50 (Attachment 1). A search of the PubMed database[1] for "antibody fragment" with a date limitation of November 30, 1998 (one day before this application was filed) retrieved 262 publications dealing with various

[1] PubMed is a service of the National Library of Medicine and includes over 14 million citations for biomedical articles back to the 1950's from both MEDLINE and from additional life science journals.

types of antibody fragments. Attachment 2 contains a sampling of abstracts from the PubMed search.[2]

Attachments 1 and 2 demonstrate that, by the filing date of this application, those skilled in the art were experienced with antibody fragments that specifically bind an antigen. Those skilled in the art would have understood that "a fragment of an antibody" as taught in Applicant's specification encompassed all such well known types of fragments.

The Office Action correctly notes that Fc fragments of antibodies are included within the recited genus of antibody fragments. Office Action at page 2. Fc receptors, to which Fc fragments bind, meet the specification's definition of a "cell surface antigen" (*i.e.*, "any antigen or receptor on a cell surface that is internalized by the cell."). Page 5, lines 13-14. Fc fragments, too, were known in the art when this application was filed. See Attachment 1.

The specification also adequately describes the recited genus of synthetic polypeptides. The specification teaches that the synthetic polypeptide specifically binds to a cell surface antigen. See page 6, lines 16-17. At the time the application was filed, numerous such synthetic polypeptides were well known in the art. Attachment 3 contains abstracts of the following publications, each of which teaches synthetic polypeptide ligands that bind to internalizing cell surface receptors:

- Weckbecker *et al.*, *Yale J. Biol. Med. 70*, 549-54, 1997 (somatostatin analog);
- Lamberts *et al.*, *Front. Neuroendocrinol. 14*, 27-55, 1993 (somatostatin analog);
- Condamine *et al.*, *J. Pept. Res. 51*, 55-64, 1998 (bombesin analog);

[2] Kipriyanov *et al.*, *Protein Eng.* 10:445-53, 1997; Riches *et al.*, *Immunology* 45:473-81, 1982; Douglas *et al.*, *Nat. Biotechnol.* 14:1574-78, 1996; and Fearon *et al.*, *J. Exp. Med.* 153:1615-28, 1981.

- Milovanovic *et al.*, *Prostate 20*, 269-80, 1992 (bombesin analog);
- Gargosky *et al.*, *Biochem. J. 247*, 427-32, 1987 (bombesin analog);
- Breeman *et al.*, *J. Nucl. Med. 37*, 108-17, 1996 (substance P analog);
- Wilson *et al.*, *Biochemistry 36*, 4542-51, 1997 (substance P analog);
- Kolodziej *et al.*, *J. Med. Chem. 38*, 137049, 1995 (cholecystokinin B analog);
- Tyler *et al.*, *Brain Res. 792*, 246-52, May 1998 (neurotensin analog);
- Gangopadhyay & Thomas, Arch Biochem Biophys. 1996 Oct 1;334(1):151-7 (carcinoembryonic antigen receptor); and
- Hoxie *et al.*, J Biol Chem. 1993 Jun 25;268(18):13756-63 (thrombin analog).

See also U.S. Patent 6,277,819, U.S. Patent 5,631,224, and U.S. Patent 6,284,725 (GLP-1 analogs); U.S. Patent 4,430,326, U.S. Patent 5,143,902, U.S. Patent 5,480,867, and U.S. Patent 5,665,705 (glucagon analogs); and U.S. Patent 6,030,940 (urokinase analogs) (copies not provided).

Attachment 3 and the patents cited above demonstrate that those skilled in the art also were experienced with numerous synthetic peptides that bound to internalizing cell surface receptors and that such synthetic peptides were well known and conventional. Thus, the specification need not describe the recited genus of synthetic peptides in detail to provide an adequate description. M.P.E.P. 8th ed., § 2163(II)(A)(3)(a).

In light of what was known in the art when the present application was filed, the specification sufficiently describes the recited genera of antibody fragments and synthetic polypeptides. Thus, the written description requirement for these genera is met. Applicant respectfully requests withdrawal of the rejection.

The Rejection of Claims 1, 3-5, 8-10, 14-20, 28, 30, 31, 35-42, and 44 Under 35 U.S.C. § 103(a)

Claims 1, 3-5, 8-10, 14-20, 28, 30, 31, 35-42, and 44 stand rejected under 35 U.S.C. § 103(a) as obvious over the abstract of Reist *et al.*, *Proc. Ann. Meet. Am. Assoc. Cancer Res. 37*, A3199, 1996 ("Reist 1996") and Zalutsky *et al.*, U.S. Patent 5,302,700 ("Zalutsky") in view of Barnett *et al.*, CA 209465 ("Barnett"), Woo *et al.*, U.S. Patent 5,130,116 ("Woo"), the abstract of Reist *et al.*, *Cancer Res. 55*, 4375-82, 1995 ("Reist 1995"), and the abstract of Wikstrand *et al.*, *Cancer Res. 57*, 4130-40, 1997 ("Wikstrand"). Applicant respectfully traverses the rejection.

The United States Patent and Trademark Office bears the initial burden of establishing a *prima facie* case of obviousness. The Office must make three showings:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be some reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

M.P.E.P., 8th ed., § 2142.

The Office Action cites six references as rendering the rejected claims obvious:

- Reist 1996 is cited as teaching that labeling an anti-EGFRvIII antibody with radiolabeled N-succinimidyl-5-iodo-3-pyridine carboxylate (SIPC) decreases the amount of radioactivity lost from a target cell after antibody internalization compared with the tyramine cellobiose method of labeling (disclosed in Reist 1995).

- Zalutsky is cited as teaching how to make SIPC and how to use it to label an anti-CEA antibody.

- Barnett is cited as teaching a carrier peptide having the property of facilitating entry of an agent into the nucleus.

- Woo is cited as teaching the advantages of internalizing radiolabeled antibodies into the nucleus for optimal killing of target cells.

- Reist 1995 is cited as teaching that anti-EGFRvIII-specific antibodies are internalized at 37°C and degraded in lysosomes.

- Wikstrand is cited as teaching that EGFRvIII is expressed on tumor cell surfaces but not on the surface of a normal cell and can be used as a selective target for delivery of anti-cancer toxins.

See pages 4 to 6 of the Office Action. The Office Action has not set forth a *prima facie* case of obviousness, however, because it does not make the required showing of a suggestion or motivation to modify the combined teaching of the cited references needed to achieve Applicant's invention.

Each of the rejected claims recites a composition for selectively internally labeling a target cell. The composition comprises three elements: (1) a ligand, (2) an oligopeptide, and (3) a label. The ligand specifically binds to a surface antigen of a cell and is internalized by the cell. The oligopeptide comprises at least one positively-charged amino acid residue and at least one D-amino acid residue. The oligopeptide is covalently bound to both the ligand and the label. The oligopeptide does not specifically bind to the surface antigen.

The Office Action asserts that it would have been *prima facie* obvious "to incorporate the carrier peptide of Barnett into the SIPC labeled L8A4 antibody" of Reist (1996). Office Action at page 6, first full paragraph. Woo, Wikstrand, and Reist 1995 are cited as providing motivation to make this combination in order to redirect delivery of the toxic label to the nucleus rather than the lysosome.

Even if, *arguendo*, the teachings of primary references Reist 1996 and Barnett were combined, however, the result would not unambiguously be the claimed composition. The rejected claims recite that the oligopeptide is covalently bound to both the ligand and to the label. There is no teaching or suggestion in either Barnett or in Reist 1996 that would direct one or

ordinary skill to place the SIPC label on the oligopeptide and not on the antibody. One of ordinary skill would need to have modified the combined teachings of the cited references to place the label on the oligopeptide. Neither Barnett, Reist 1996, nor any of the other cited references teaches or suggests this modification. The teaching to use an antibody to target a cell and an oligopeptide to carry a label comes only from Applicant's specification, not from the cited references.

The claimed invention solves two problems: (1) how to specifically label desired target cells but not the surrounding cells and (2) how to improve label retention by the specifically targeted cells. The invention solves these problems by providing a composition comprising a ligand which specifically binds to a cell surface antigen of a cell and is internalized by the cell, an oligopeptide with particular recited characteristics which is covalently bound to the ligand, and a label which is covalently bound to the oligopeptide:

> It is a discovery of the present invention that conjugation of radiolabels to ligands that bind to cell surface antigens via positively charged, proteolysis-resistant oligopeptides improves the effectiveness of radioimmunotherapy. Selective localization and retention of radiolabel within a class of target cells is increased using such oligopeptides.

Specification at page 5, lines 2-6. The specification teaches that the oligopeptide in the claimed compositions prevents the label from diffusing out of the lysosome following ligand degradation: "D-amino acids render the oligopeptide more resistant to lysosomal proteases . . . , thereby improving retention of the label within the target cells and limiting release of the label and its subsequent reuptake by other cells." Specification at page 6, line 31 to page 7, line 3 (references omitted). In contrast, the cited primary references provide no motivation to combine the Barnett peptide with the Reist 1996 SIPC-labeled antibody and to place the label on the peptide.

Neither Barnett nor Reist 1996 provides a motivation to combine the Barnett oligopeptide with the Reist 1996 SIPC-labeled antibody at all, much less to modify the placement of the label on the resultant composition. Barnett teaches that the disclosed peptide facilitates entry of an agent into cells and subsequent localization in the nucleus. Barnett, page 2, lines 6-7. Barnett also teaches, however, that the carrier peptide does not specifically target any particular cell or tissue type: "These studies demonstrate rapid and efficient distribution of the carrier peptide to all major organs of the injected animal." Barnett at page 12, lines 12-13. In contrast, claim 1 as amended explicitly recites a composition for "selectively internally labeling a target cell." Given the nature of one of the problems to be solved – how to specifically label target cells but not the surrounding cells -- the ordinary artisan would not have thought to combine the Barnett peptide, which is distributed to cells non-specifically, with the Reist 1996 SIPC-labeled antibody, which will specifically target EGFRvIII-expressing cells.

The additional references cited in the Office Action do not provide the required motivation. The teachings of the cited references must be considered as a whole and compared with the subject matter of the rejected claims. *Graham v. John Deere* 383 U.S. 1, 17 (1966). Neither Zalutsky, Woo, Reist 1995, or Wikstrand contains even a hint to combine an antibody with any type of oligopeptide, much less to put a label on an oligopeptide rather than the antibody. Thus, none of these references provides the motivation needed to support the asserted *prima facie* case of obviousness.

The teaching to make the recited composition comes only from Applicant's specification. Absent improper hindsight reconstruction, the teachings of the cited references cannot be combined to suggest what the present specification teaches.

The cited combination of references does not teach or suggest the claimed composition. Thus, the Office Action has not established a *prima facie* case of obviousness.

Applicant respectfully requests withdrawal of the rejection.

The Rejection of Claims 1, 3-6, 8-10, 14-20, 28, 30, 31, 35-42, and 44-47 Under 35 U.S.C. § 103(a)

Claims 1, 3-6, 8-10, 14-20, 28, 30, 31, 35-42, and 44-47 stand rejected under 35 U.S.C. § 103(a) as obvious over Reist 1996, Zalutsky, Barnett, Woo, Reist 1995, and Wikstrand in view of Schlom, in *Molecular Foundations of Oncology*, pp. 95-134, 1991 ("Schlom"). Applicant respectfully traverses the rejection.

As discussed above, the Office Action cited all of these references but Schlom to reject claims 1, 3-5, 8-10, 14-20, 28, 30, 31, 35-42, and 44. Schlom appears to be added to extend the rejection to claims 6 and 45-47.

Claims 6 and 45-47 depend from claim 1, which recites a ligand which specifically binds to a surface antigen of a cell and is internalized by the cell. Claim 6 recites that the ligand is an interspecies recombinant antibody. Claim 45 recites that the ligand is a fragment of an antibody comprising a portion of an immunoglobulin light chain variable region and a portion of an immunoglobulin heavy chain variable region. Claim 46 recites that the ligand is a single chain Fv fragment of an antibody. Claim 47 recites that the ligand comprises a single chain Fv fragment of an antibody. Schlom is cited as teaching that single chain Fv antibodies are better able to penetrate a tumor mass, avoid induction of a human antimurine antibody (HAMA) response, and clear the blood more rapidly than whole antibodies. Office Action, page 7, second full paragraph.

The deficiencies of the rejection based on Reist 1996, Zalutsky, Barnett, Woo, Reist 1995, and Wikstrand are discussed above. Schlom's disclosure of the advantages of single chain Fv antibodies does not cure these deficiencies. Schlom does not teach or suggest combining a labeled antibody with an oligopeptide and changing the location of the label from the antibody to the oligopeptide. In fact, Schlom actually teaches away from the claimed invention. Schlom teaches use of a labile linkage between an antibody and a label so that the label, once separated from the antibody, can enter the target cells as well as the surrounding cells: "[T]he chemical bond utilized to link the drug to the immunoglobulin is sufficiently labile to permit dissociation of the cytotoxic agent at the tumor cell periphery followed by transport into the antigen-positive or nearby antigen-negative cell." Schlom at page 107, column 2, second paragraph. Schlom's teaching of the desirability of labeling both target and non-target cells is in direct contrast to the function of the claimed composition, which results in selective labeling of target cells, as recited in claim 1. Thus, Schlom does not support a *prima facie* case of obviousness that claims 1, 3-6, 8-10, 14-20, 28, 30, 31, 35-42, or 44-47 are obvious.

The cited combination of references does not teach or suggest the claimed composition. Thus, the Office Action has not established a *prima facie* case of obviousness. Applicant respectfully requests withdrawal of the rejection.

The Rejection of Claims 1, 3-6, 7-10, 14-20, 28, 30, 31, 35-42, and 44-47 Under 35 U.S.C. § 103(a)

Claims 1, 3-6, 7-10, 14-20, 28, 30, 31, 35-42, and 44-47 stand rejected under 35 U.S.C. § 103(a) as obvious over Reist 1996, Zalutsky, Barnett, Woo, Reist 1995, and Wikstrand in view of Schlom, in *Molecular Foundations of Oncology*, pp. 95-134, 1991 ("Schlom"). Applicant respectfully traverses the rejection.

As discussed above, the Office Action cited all of these references but Schlom to reject claims 1, 3-5, 8-10, 14-20, 28, 30, 31, 35-42, and 44. Schlom appears to be added here to extend the rejection to claim 7.

Claim 7 depends from claim 1, which recites a ligand which specifically binds to a surface antigen of a cell and is internalized by the cell. Claim 7 recites that the ligand is a humanized antibody. Schlom is cited as teaching, *inter alia*, that use of humanized antibodies can circumvent the induction of a human antimurine antibody (HAMA) response. Office Action, paragraph bridging pages 7 and 8.

The deficiencies of the rejection based on Reist 1996, Zalutsky, Barnett, Woo, Reist 1995, Wikstrand, and Schlom are discussed above. Schlom's disclosure of the advantages of using humanized antibodies does not cure these deficiencies. In addition, as mentioned above, Schlom teaches that one should label both target and non-target cells. This teaching is in direct contrast to how the claimed composition functions, *i.e.*, it selectively labels target cells, as recited in claim 1. Thus, Schlom does not support a *prima facie* case that claim 7 or claims 1, 3-6, 8-10, 14-20, 28, 30, 31, 35-42, or 44-47 are obvious.

The cited combination of references does not teach or suggest the claimed composition. Thus, the Office Action has not established a *prima facie* case of obviousness. Applicant respectfully requests withdrawal of the rejection.

The Rejection of Claims 1, 5, 8-10, 14-16, 21, 28, 30, 35-37, 43, and 44 Under 35 U.S.C. § 103(a)

Claims 1, 5, 8-10, 14-16, 21, 28, 30, 35-37, 43, and 44 stand rejected under 35 U.S.C. § 103(a) as obvious over Reist 1996 in view of Barnett, Woo, Reist 1995, Wikstrand, and Schmidt *et al.*, U.S. Patent 4,614,723 ("Schmidt"). Applicant respectfully traverses the rejection.

As discussed above, the Office Action cited all of these references but Schmidt to reject claims 1, 3-5, 8-10, 14-20, 28, 30, 31, 35-42, and 44. Schmidt appears to be added to extend the rejection to claim 21.

Claim 21 depends from claim 1, which recites a label which is covalently bound to an oligopeptide. Claim 21 recites that the label is fluorescent. Schmidt is cited as teaching various porphyrin fluorescent labels for conjugation to antibodies. Office Action, page 9, second paragraph.

The deficiencies of the rejection based on Reist 1996, Zalutsky, Barnett, Woo, Reist 1995, and Wikstrand are discussed above. Schmidt's disclosure of porphyrin fluorescent labels does not cure these deficiencies. Schmidt teaches attaching the porphyrin fluorescent labels to the antibodies using a cross-linking agent: "The coupling of the above-mentioned porphyrin derivative with anti-CEA [antibodies] was carried out as described below with the aid of the water-soluble carbodiimide derivative 1-cyclohexyl-3-(2-morpholinoethyl)-carbodiimide methyl-p-toluenesulphonate." Schmidt column 10, lines 6-10. Following the teachings of Schmidt, one